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EDITORIAL

Sorafenib and entecavir: The dioscuri of treatment for advanced hepatocellular carcinoma?

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Abstract

Hepatitis B virus (HBV) is responsible for 50%-80% of cases of hepatocellular carcinoma (HCC) worldwide. Entecavir (ET) is a potent inhibitor of chronic HBV-DNA polymerase, inhibiting both the priming and elongation steps of viral DNA replication. Sorafenib (SO) has proven efficacy in prolonging survival in patients with advanced HCC. In this frontier report we discuss a possible way to optimize treatment outcomes in patients with HBV and HCC by treatment with ET and SO, on the basis of our practice and published evidence from the literature.

Key words: Entecavir; Hepatocellular carcinoma; Hepatitis B virus; Liver function; Sorafenib

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INTRODUCTION

Over 350 million people globally are chronically infected with hepatitis B virus (HBV) and around 25% of these will develop hepatocellular carcinoma (HCC)[1,2]. HCC is the fifth most common malignancy with approximately 750 000 new cases occurring worldwide each year[3,4]. Overall 70%-90% of patients with HCC have liver cirrhosis caused mainly by HBV and hepatitis C virus[5,6]. HBV, an oncogenic virus, can cause HCC in the absence of cirrhosis and the risk of HBV-induced HCC varies depending on the presence or absence of concomitant cirrhosis. Chronic carriers of HBV have up to a 30-fold increased risk of HCC[7]. In areas of high HBV endemicity, persons with cirrhosis have an approximately 16-fold higher risk of HCC than the inactive carriers, and a 3-fold higher risk for HCC than those with chronic hepatitis but without cirrhosis[8]. While epidemiological studies provide strong evidence for a causal role of chronic HBV infection in the development of HCC, the pathogenesis of HBV infection and carcinogenesis of HBV-associated HCC are still not fully understood. It is thought that HBV exerts its oncogenic potential through both indirect and direct mechanisms that may act in synergy[9-11].

In this frontier report we discuss a possible way to optimize treatment outcomes in patients with HBV and HCC by treatment with entecavir (ET) and sorafenib (SO), on the basis of our practice and published evidence from the literature.

POTENTIAL ROLE OF ET AND SO

The most effective way to prevent HBV-related HCC is by vaccination but in patients already infected with HBV, antiviral therapy is the best strategy[9]. ET, a cyclopentyl guanosine analog, is a potent inhibitor of chronic HBV-DNA polymerase, inhibiting both the priming and elongation steps of viral DNA replication. In clinical trials, ET was superior to lamivudine for all primary end points

evaluated in both nucleoside-naive and lamivudine-resistant patients as well as being effective in both hepatitis B "e" antigen-positive and -negative nucleoside-naive patients. Antiviral therapy can reduce, but not eliminate the risk of HCC especially in patients with pre-existing cirrhosis and it is therefore important to maintain virological remission. The use of ET allows long-term HBV-DNA suppression with a low risk of resistance.

SO, a tyrosine kinase inhibitor, has been demonstrated in two large scale randomized, double-blind, placebo-controlled, multicentre, phase Ⅲ trials (the SHARP trial and the Asia-Pacific trial) to prolong median overall survival and delay the median time to progression in patients with advanced HCC[12,13]. The SHARP study was the first to show an overall survival benefit for SO in patients with advanced HCC, in which the overall survival was 10.7 mo[14]. Subanalyses of the SHARP population based on a range of parameters including aetiology (hepatitis B virus present/absent); tumour burden (macroscopic vascular invasion and/or extrahepatic spread present/absent); presence or absence of either lung or lymph node metastasis at baseline, confirmed the efficacy and safety of SO in these subpopulations indicating that SO is effective for patients from the AP region with advanced HCC, irrespective of baseline status[15,16].

Individually ET and SO have been demonstrated to have important roles in the management of patients with HBV and HCC but how best should we use these agents - in combination or as a sequential strategy. The problem is that although there are a number of published guidelines on the treatment of patients with HBV there are no precise indications on the use of antiviral agents in patients with HBV-related HCC, however it is recognized that the goal of antiviral therapy for HBV is to preserve liver function and prevent the development of cirrhosis and HCC. Early intervention is therefore necessary to prevent liver cell damage and decrease viral genome integration. We believe that it is vital to prevent the deterioration of liver function as modulation of liver function may affect survival directly and indirectly but also it may have an impact on the patient's ability to tolerate subsequent treatments.

In a study by Jin *et al*[17], first-line ET monotherapy was effective in HBV patients (with and without HCC), improved hepatic function and importantly was associated with increased survival after eradication of HCC - confirming previous results that it improved liver function in patients with decompensated cirrhosis[18,19]. Considering that liver function is a key factor in deciding treatment options for a given patient and concomitant liver dysfunction often hampers both curative and palliative therapies, the fact that ET can improve hepatic function is decisive in the clinical scenario[20]. Furthermore, in a study by Chang *et al*[21] the majority of nucleoside-naive patients with HBV who were treated with long-term ET achieved substantial histological improvement together with regression of fibrosis or cirrhosis. SO has also shown promising antifibrotic activity with efficacy at relatively low doses at the early stage of liver fibrosis[22].

Table 1 Baseline characteristics and main treatment outcomes of our cohort (*n* = 15) *n* (%)

Baseline characteristics	Value
Characteristic	
Male	1 (6.7)
Age, yr (range)	67 (62-76)
BCLC stage	
B - intermediate	10 (66.7)
C - advanced	5 (33.3)
Child-Pugh score	
5	6 (40)
6	9 (60)
Treatment outcomes	
Overall survival, mo (range)	26.5 (10-36)
Liver decompensation	4 (26.7)
Hepatocellular carcinoma progression	3 (20.0)
Interruption of sorafenib therapy due to adverse events	0 (0)

All subjects achieved viral clearance following entecavir treatment before the initiation of sorafenib 800 mg/d.

OUR EXPERIENCE

In our unit, we treated a total of 15 patients (1 male; aged 62-76, median 67 years) with advanced HCC and a history of HBV cirrhosis from October 2008 to December 2011. Diagnosis of advanced HCC was made according to the Barcelona Criteria using contrast enhanced ultrasound, elevated values of alpha-fetoprotein and/or liver biopsy. Ten patients had intermediate BCLC stage B and 5 had advanced BCLC stage C and all had Child Pugh A (9 with an A6, 6 with A5). The baseline characteristics of patients are summarized in Table 1.

All patients achieved a complete clearance of HBV-DNA following the administration of ET (0.5 mg/d) before the initiation of SO. The dosage of SO was gradually increased over a 6-wk period to reach the recommended dosage of 800 mg/d.

The median survival in these patients with HCC and HBV was 26.5 mo (range 10-36 mo). No patient stopped therapy due to AEs (cardiac, gastrointestinal, haematological, neurological or dermatological, or endocrinological). All patients had blood pressure within the accepted recommend range, assumed regular cardiac medication as necessary and were negative for HBV-DNA. Four patients had liver decompensation and three had progression of HCC.

It must be emphasized that our experience is reported here in a very synthetic form, since this paper should be intended as a short commentary addressing how treatment with SO and ET might optimize treatment outcomes in patients with HBV and HCC. In addition, the data reported here present several limitations, which should be taken into account to put the above-mentioned findings in a proper framework. First, the sample observed in our experience is too limited to draw any conclusion. Second, the pure observational nature of our findings does not

allow to retrieve any definite cause-effect relationship.

These limitations taken into account, these results are somehow encouraging: this may be, at least in part, due to the viral clearance achieved by patients. We cannot rule out, however, that the longer survival observed in our patients can be attributed to the high proportion of subject with BCLC-B stage HCC.

CONCLUSION

On the basis of our experience and current literature, therefore, we propose that in patients with HBV monotherapy with ET should be given initially to reduce viral load and preserve liver function thereby allowing follow-up treatment with SO to treat HCC. We believe that this treatment approach may represent a potential improvement in the current management of advanced HCC in patients with concomitant HBV infection. However, further, well-designed studies are needed to investigate the efficacy and safety of this therapy in a large sample of patients. If such study will provide positive results, we feel that SO and ET will be considered the "Dioscuri", the warrior twins of the Greek mythology, of the treatment of advanced HCC.

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